REMARKS

Claims 1 to 54 are pending. Claims 1 to 3 and 10 to 14 were examined in this Office Action. No amendments are proposed at this time.

Prosecution in Related Applications

Applicants enclose herewith (as Appendix 1) for the Examiner's review an Interview Summary, versions of which were received by applicants in certain related cases, i.e., U.S. Serial Nos.10/177,930; 10/053,535; 10/367,277; 10/371,666; 10/413,817; 10/439,632; 10/455,564; and 10/600,182. This particular Interview Summary was received by applicants in U.S. Serial No. 10/439,632. Applicants' representatives (the undersigned and Todd E. Garcia) conducted an Interview with Examiner Yvonne L. Eyler on February 21, 2007 (the "Interview"). During the Interview, the claims of applicants' various applications relating to carbon monoxide (CO) were discussed with regard to their compliance with the enablement requirement. In the attached Interview Summary, related applications 10/053,535, 10/367,277, 10/600,182, 10/177,930, 11/401,722, 10/413,817, 10/371,666, 10/676,280 and 10/455,564 are recited, but the present application is not. Applicants believe the present application should have been included as well, so to expedite prosecution applicants address the substance of the Interview in the context of the present claims.

In the Interview, Examiner Eyler explained that the Office, following an internal meeting among Examiners of the related applications, has concluded that Mayr et al. (Am. J. Resp. Crit. Care Med., Vol. 171, p. 354-360, 2005 (hereinafter "Mayr")), Ryter et al. (Curr. Opin. Pharmacol., Vol. 6, p. 257-262, 2006 (hereinafter "Ryter")), Dolinay et al. (in *Breath Analysis for Clinical Diagnosis and Therapeutic Monitoring,* Amann and Smith, eds., World Scientific Publishing Company (2004), p. 203-236 (hereinafter "Dolinay")), and Choi et al. (Am. J. Resp. Crit. Care Med., Vol. 171, p. 1318-1319, 2005 (hereinafter "Choi"))[1] raise questions regarding scope of enablement for claims directed to treating human conditions with carbon monoxide (CO). Examiner Eyler indicated that U.S. Serial Nos. 10/053,535, 10/413,817, 10/439,632,

[1] Each of these post-filing date publications was made of record in the present case in an Information Disclosure Statement filed August 21, 2006.

10/371,666, and 10/455,564 (again, applicants believe the present application should have been included as well) either have or will receive Office Actions that describe the alleged enablement issues. Examiner Eyler also indicated that those issues do not apply to claims drawn to administering CO to organ donors, which claims are pending in U.S. Serial Nos. 10/600,182, 10/177,930, and 11/401,722.

The present Office Action does not cite Mayr, Ryter, Dolinay or Choi as raising any enablement issues, and does not opine that there is any reason to doubt that CO can be efficacious in human therapy. Nevertheless, in order to ensure that no such ground for rejection is belatedly asserted in a future Office Action, thereby delaying issuance of the present claims, applicants enclose herewith (as Appendix 2) for the Examiner's review a copy of a Reply filed in U.S. Serial No. 10/439,632 on June 11, 2007 (the "Reply"). In the Reply, applicants address in detail the concerns raised by the Office in the Interview Summary discussed above. *See in particular the portion of the Reply from page 3, line 3, through page 12, line 6.* Though the conditions treated and rodent models utilized in the present application of course differ from those of U.S. Serial No. 10/439,632 discussed in the Reply, the arguments presented in that Reply would generally apply to the present application if the same enablement rejection were to be asserted in the present application. Applicants urge the Examiner to acknowledge for the record that in view of the evidence and arguments presented in that Reply, the scope of enablement issue raised in the Interview Summary will not be applied against the present claims.

Applicants now turn to the rejections raised in the present Office Action.

Rejections under 35 USC §112, paragraph 1

Claims 1 to 3 and 10 to 14 (i.e., all of the claims presently under examination) were rejected for allegedly failing to comply with the enablement requirement. The Office asserts that applicants have not enabled the full scope of the pending claims, despite applicants' detailed disclosure and the *in vivo* data provided in the specification. Specifically, the present Office Action states (beginning at page 4):

> Carbon monoxide (CO) is known in the art to be toxic to humans causing exhaustion and headache at levels of as low as 70 ppm (Omaye, "Metabolic modulation of carbon monoxide toxicity," in Toxicology 180 (2002) 139 – 150). The instant specification at paragraph [0400] talks about using Co at levels of 10 ppm to 3000 ppm for the treatment of hemorrhagic shock.
>
> * * *
>
> It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific guidance is required to enable the artisan to practice the full scope of the claimed invention.
>
> In the instant case, the scope of the claimed invention spans all concentrations of CO for effectively treating hemorrhagic shock. Also, while the instant disclosure at paragraph [0400] envisions the use of 10-3000 ppm CO for inhalation, the prior art describes CO to be toxic at levels as low as 70 ppm.
>
> * * *
>
> One of ordinary skill in the art would first need to determine what concentration of CO to use that would not provide toxicity since applicants envision concentrations of 10-3000 ppm and Omaye discloses that CO levels of 70 ppm is toxic ands the claims is open ended to any amount of CO.
>
> * * *
>
> This rejection can be overcome by the concentration of CO effective for claimed method. (*Informal English in the original*)

Applicants respectfully traverse and submit that the claims are presently in full compliance with the enablement requirement. The facts that CO is potentially toxic and that Omaye (Toxicol. 180:139-150 (2002) (hereinafter "Omaye")) describes side effects a person might experience when exposed to various levels of CO do not justify requiring that applicants limit their claims to administering specific amounts of CO. There is no question that CO can be toxic to various degrees when, for example, a high concentration of the gas is inhaled for a prolonged period of time in an uncontrolled manner. Indeed, the newscasts and medical books abound with reports of people being killed in their automobiles by overexposure to exhaust

fumes and in their homes by CO released from improperly installed furnaces. The side effects of exposure to CO are well documented. However, applicants ask that the Office look beyond the negative reputation of CO and truly consider the present invention for what it is: controlled administration of CO to patients to treat HS. The potential toxicity of CO and the side effects an individual may or may not experience upon exposure to it are simply irrelevant to the Office's proper determination of whether applicants' claims comply with United States patent law.

The fact that CO, like almost all drugs, is potentially toxic and may cause side effects doesn't mean that skilled practitioners would have to carry out undue experimentation in order to perform the claimed methods. On the contrary, when bringing a therapeutic agent from laboratory studies to the clinic, skilled practitioners routinely perform intensive studies to determine optimal doses of potentially toxic substances. Critical information is gleaned from preclinical animal studies, but often, substantial dosage adjustments (i.e., dosage amounts, duration of exposure, etc.) are required before a drug is deemed by the FDA and medical community to be safe and effective in humans. Along the way, it is not unusual for researchers to publish conflicting, and even contradictory, data about the safety and efficacy of a drug as it is studied in laboratories throughout the world. Even after the research is completed, the drug is FDA approved, and prescription guidelines are communicated to the medical community, physicians must often adjust the dosage of the drug at the time of prescribing based on, e.g., a patient's age, weight and medical history. This is nothing more than expected, routine, reasonable experimentation in the arts of drug development and medicine. It is not experimentation that is in any way "undue" for this compound any more than for any other. The fact that Omaye describes some side effects that people exposed to various levels of CO might experience does not logically support a proposition that practitioners would have been unable to use their skill in this instance to perform the presently claimed methods.

Further, the Office cites *In re Fisher* to support its proposition that "the pharmaceutical art is unpredictable, **requiring each embodiment to be individually assessed for physiological activity**" (Office Action at page 4, emphasis added). The Office apparently believes that applicants are required in this instance to show, e.g., in a working example, that each dose

encompassed by applicants' claims works to treat HS without inducing any side effects. Such a standard is not supported by *Fisher*. On the relationship between claim scope and enablement, *Fisher* states that "[i]n cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." The Manual of Patent Examining Procedure (M.P.E.P.) elucidates the Office's understanding of Fisher at §2164.06, stating:

> The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling.

Nowhere does *Fisher* or the M.P.E.P. mandate the extraordinarily stringent standard proposed by the Office here. In providing a detailed specification that teaches how to administer CO to treat HS (which includes proof-of-concept experimentation *in vivo* in rodent models) and in view of the fact that there was a vast wealth of information available in the art about CO (see discussion below), applicants have more than met their burden of enabling skilled practitioners to carry out the claimed methods.

At this juncture, given that the Office Action refers to the *Wands* factors, applicants believe it appropriate to review the legal standard for enablement and to show how that standard applies to the pending claims. The enablement requirement of 35 U.S.C. § 112, paragraph 1, is satisfied so long as the disclosure contains sufficient information so that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention without undue experimentation. *In re Wands*, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988). The Office must consider several factors when deciding whether or not a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." The factors

include: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the relative skill of those in the art; (5) the predictability or unpredictability of the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. *Id.* See also MPEP § 2164.01(a). Applicants respectfully submit that a careful consideration of the factors enumerated in *Wands* would lead the Office to the inescapable conclusion that skilled practitioners would be able to practice applicants' claimed invention without undue experimentation. Applicants address the *Wands* factors below.

The Nature of the Invention

According to MPEP § 2164.05(a), "The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art." In the present case, the nature of the invention is the administration of a potentially toxic pharmaceutical gas to treat a disorder.

The Presence or Absence of Working Examples

The specification provides *in vivo* working examples at pages 18 to 24. There, applicants demonstrated that 250 ppm inhaled CO can be used to prevent multiple organ injury in a rodent model of HS/R (see carryover paragraph of pages 20-21 in the application as filed) .

The Amount of Direction or Guidance Provided

The specification throughout provides detailed and useful guidelines for administering CO to patients. For example, the specification teaches how to make CO compositions for delivery to a patient (see, e.g., page 9, line 14, to page 11, line 25). It also teaches how to deliver CO to patients and what variables to consider when choosing a dosage regimen (see, e.g., page 11, line 26, to page 15, line 30). Dosage amounts are also discussed throughout the specification, e.g., at page 8, line 10, to page 9, line 12, as well as at page 20, line 30, to page 21,

line 9, which discloses that 250 ppm was used in the working examples. Applicants have clearly presented a sufficient amount of direction and guidance for skilled practitioners who wish to carry out the claimed methods.

The Reply attached hereto as Appendix 2 includes a number of Exhibits; the one labeled "Exhibit D" is a post-filing date published clinical protocol[2] describing a method of delivering CO that is encompassed by the teachings of the present specification. For example, Exhibit D (at page 1, para. 4) states:

> [S]ubjects are treated with either CO or room air (placebo) for 6 hours. (Subjects in the pilot study receive treatment for only 3 hours). The gas is delivered through a cushioned mask placed over the nose and mouth. The amount of exhaled CO is measured before, during, and after inhalation of the gas.

Such a protocol is easily derivable from applicants' specification, which states, for example:

> A CO-containing gas mixture is prepared as above to allow passive inhalation by the patient using a facemask or tent. (page 13, lines 22 and 23);
>
> Gaseous CO compositions are typically administered by inhalation through the mouth or nasal passages to the lungs, where the CO is readily absorbed into the patient's bloodstream. (page 12, lines 13 to 15); and
>
> The patient's CO level can be monitored by studying (1) carboxyhemoglobin (COHb), which can be measured in venous blood, and (2) exhaled CO collected from a side port of the ventilator. CO exposure can be adjusted based upon the patient's health status and on the basis of the markers. (page 13, lines 12 to 15).

Exhibit D's protocol is one contemplated and taught by applicants in their specification. It is evidence that skilled practitioners, based on the teachings of the specification and the

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[2] Exhibit D is not prior art, but U.S. law permits reference to non-prior art publications to demonstrate that the claimed invention would have been operable for its intended purpose. See, e.g., *Gould v. Quigg*, 3 U.S.P.Q.2d 1302, 1305 (Fed. Cir. 1987) ("As to the technical article, it is true that a later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling. In this case, the later dated publication was not offered as evidence for this purpose. Rather, it was offered as evidence of the level of ordinary skill in the art at the time of the application and as evidence that the disclosed device would have been operative.").

knowledge of those of ordinary skill in the art, would have been able to practice the invention without undue experimentation, despite the facts that CO is a potentially toxic molecule and that applicants' methods had not been tested in humans as of the filing date of the present application.

The Predictability of the Art

According to the MPEP at section 2164.03,

> the 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art.

While the art did not disclose use of CO to treat HS, it did provide ample teachings about the toxic effects of various levels of CO. Since this appears to be the point that concerns the Examiner (see multiple references on pages 4 and 5 of the Office Action to Omaye's mention that 70 ppm CO can produce headaches), applicants will address the toxicity issue in some detail. However, applicants first remind the Examiner that the mere fact that 70 ppm CO can produce headaches when inhaled for at least an hour does not mean that 70 ppm or even higher levels cannot be used therapeutically. As those in the medical arts know, many "toxic" drugs are highly useful for treating conditions where the potential therapeutic outcome justifies the risk of toxic side effects. A transient headache seems like a relatively minor risk, particularly in a patient who is likely unconscious from the loss of blood that HS entails.

Given the extensive body of literature that existed at the time the present application was filed, the detailed teachings of the specification and the level of skill of practitioners in the fields of medicine and drug development, skilled practitioners would have appreciated that a CO treatment regimen might have to be routinely adjusted to take into account certain variables, e.g., the type of patient (e.g., human, dog, rat, etc.) and the size, age, and condition of the patient. However, skilled practitioners would have had no reasonable basis for doubting that the claimed methods would work, despite a potential need for such routine adjustments. Once applicants showed that the methods worked in one species, skilled practitioners would clearly have been able to predict that a similarly successful outcome would very likely be achievable in others,

even though routine experimentation, e.g., to account for differences between species, might be required. The publication cited by the Office, Omaye, does not provide evidence that the art of administering CO to patients is any more unpredictable than the art of administering any other new drug. The fact that Omaye reports various side effects an individual may experience from CO exposure does not somehow negate the fact that applicants' specification provides detailed information about how to administer CO to treat patients and that the literature is rich with information to guide practitioners in doing so. Any experimentation that may be required to perform the claimed methods would therefore have been routine and not in anyway "undue."

The State of the Prior Art

The state of the prior art is what skilled practitioners knew about the claimed subject matter at the time the present application was filed. In this case, as the Examiner is no doubt aware, there existed an extensive body of literature describing the toxicity (or lack thereof) of various levels of CO. The prior art teaches, *inter alia*, that (i) CO's toxic effects can be correlated to blood carboxyhemoglobin (COHb) saturation; (ii) CO's toxicity at a given concentration depends on known factors (e.g., age, health, etc.); and (iii) blood COHb saturation is highly predictable and easily measurable. To illustrate, applicants present here for the Examiner's benefit just a small sample of useful articles that make up that vast body of literature.

Experimental administration of CO to humans and animals has been practiced for many years in the context of pollution studies. The book Medical Toxicology, Diagnosis and Treatment of Human Poisoning, Ellenhorn and Barceloux (Eds.) Elsevier, 1988, contains a chapter entitled "Carbon Monoxide" at pages 820-829 (copy attached as Appendix 3) discussing the toxic effects of various levels of CO inhaled for various time periods. See, for example, Table 34-1, in which various concentrations of CO and % of COHb are correlated with physiological symptoms. Particularly pertinent is Figure 34-1, a graph illustrating the categories of physiological effects one can expect when various concentrations of CO are inhaled for different time periods. Clearly the art understood from evidence such as this what concentrations could be inhaled for what time period (e.g., 0.02% CO (i.e., 200 ppm) for 1 hour) and still

produce "no noticeable effects." If "headaches and nausea" could be tolerated during the treatment period (and for an unconscious patient suffering from HS, headaches and nausea would seem to be trivial side effects that would not deter treatment with a life-saving compound), then according to this graph, the dosing could be increased to 200 ppm for over 4 hours, or perhaps 1600 ppm or higher for a short period such as 1/2 hour. The point is that the art was well aware of what doses of CO could be tolerated for what periods of time without dangerous toxic effects, and could use that information to avoid a dosing regimen that risked unduly dangerous effects.

Furthermore, the COHb level of an individual administered a specified amount of CO for a period of time is highly predictable, and COHb level and toxic effects can easily be monitored during administration. Stewart, 1974, "The Effects of Low Concentrations of Carbon Monoxide in Man," Scand. J. Respir. Dis. Suppl. 91:56-62 (submitted herewith as Appendix 4), indicates that "the amount of carbon monoxide absorbed during exposure is highly predictable," and provides a chart showing predicted and experimental values of COHb accumulation over time for four CO concentrations (see Figure 1). Wright and Shephard, 1979, "Physiological effects of carbon monoxide," Int. Rev. Physiol. 20:311-68 (submitted herewith as Appendix 5), provides additional guidance to skilled practitioners regarding methods of experimentally administering controlled amounts of CO to individuals (p. 324-325) and methods of monitoring CO and COHb levels (p. 320-324). Wright and Shephard teach that COHb can be measured directly in blood or indirectly by measuring exhaled CO. Vreman et al., 1995, "Carbon monoxide and carboxyhemoglobin," Adv. Pediatr. 42:303-34 (submitted herewith as Appendix 6) provide more guidance regarding the monitoring of CO in the blood and breath, and indicate that blood lactate levels may also be useful as an indirect measure of CO toxicity. Through routine monitoring of a patient during CO administration to ensure that overdosing does not occur, the risks of toxicity can be minimized.

Furthermore, at the time the present application was filed, CO was being administered (apparently safely) in hospitals and clinics across the country in conjunction with a common test for pulmonary function. The CO diffusing capacity (DL_{CO}) test measures the permeability of the lungs to gases. In one variant of this test, the subject inhales a single breath of a gas mixture

containing 0.3% (3000 ppm) CO, holds his or her breath for ten seconds, and then exhales (American Thoracic Society, 1987, "Single Breath Carbon Monoxide Diffusing Capacity (Transfer Factor): Recommendations for a Standard Technique," Am. Rev. Respir. Dis. 136:1299-1307; submitted herewith as Appendix 7). The proportion of CO exhaled is measured and used to estimate the subject's lung diffusion capacity. Despite the very high concentration of CO utilized in this test, the risk is apparently deemed acceptable in view of the perceived benefits of obtaining the test results.

These publications are but a small sample of the art regarding CO. The literature was thus incontrovertibly rich with information regarding what levels of CO exposure can produce what sorts of toxicity in humans and animals, ways to monitor and counter the toxic effects of CO, and methods of determining CO levels in patients, estimating CO uptake, and administering CO to patients for testing pulmonary function. Skilled practitioners would have been guided by the above and other literature, along with the present specification, in determining what amounts of CO would be safe, yet effective, to treat hemorrhagic shock. This is certainly more information than typically exists, for example, in support of newly-invented cancer treatments, which not infrequently involve inherently toxic (and even poisonous) substances, yet nonetheless are considered useful.

Further, the art recognized that another potentially toxic gas, nitric oxide (NO), could be used as a therapeutic in humans, including infants. Nitric oxide was approved for pharmaceutical use by the FDA in December of 1999 after six years of clinical trials (see, e.g., http://www.touchbriefings.co.uk/pdf/790/ino.pdf). Since then this has become an important, lifesaving therapeutic for so-called "blue babies," i.e., newborns in respiratory distress due to hypoxic respiratory failure.[3] These "blue babies" – owing their blue color to lack of oxygen in their blood – miraculously turn a healthy pink when they inhale NO gas. Applicants mention this because it is evidence that those of skill in the art understood that toxic gases can be useful therapeutics when properly handled.

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[3] The physicians who invented the nitric oxide treatment were given the 2003 Inventor of the Year award by the Intellectual Property Owners Association for this lifesaving contribution to the medical sciences. One of their issued patents is U.S. Patent No. 5,485,827.

The Relative Skill of Those in the Art

In the present case, "those in the art" would have been health care practitioners, e.g., physicians. Applicants submit that health care practitioners at the priority date had a high level of skill in administering drugs (even potentially toxic ones) to patients. To illustrate, one could point to any number of highly toxic compounds, such as cancer chemotherapeutics, inhaled oxygen (which can cause oxidative stress and lung damage), and inhaled anesthetic gases, all of which can be dangerous in overly high doses. These substances are routinely successfully administered by physicians of ordinary skill, and provide undeniable benefit to patients.

Again, one particularly useful example is that of NO gas. NO is an FDA-approved pharmaceutical agent that bears many similarities to CO. Both are colorless and odorless gases that are products of combustion and commonplace components of air pollution and cigarette smoke. Like CO, NO binds to and inactivates hemoglobin. NO has the additional danger (not found with CO) of being a chemically highly reactive molecule. NO readily reacts with oxygen (e.g., in the air) to yield NO_2, which in turn forms extremely corrosive and dangerous nitric acid when it reacts with water (e.g., in the lung). Since CO does not exhibit anything like that level of reactivity, NO gas arguably has an even higher level of potential toxicity than does CO. Yet, despite all of the potential dangers of NO, it was approved for pharmaceutical use by the FDA in 1999 and since then has become an important, lifesaving therapeutic. The very real potential toxicity of NO requires careful attention to proper clinical use, but this certainly has not proven to be a barrier to widespread, successful use of NO-based therapy in hospitals around the world. This illustrates that healthcare practitioners of ordinary skill at the present application's filing date knew how to manage appropriate medical use of potentially toxic medical gases.

The Quantity of Experimentation Necessary

In order to determine effective amounts of CO for human or other patients, skilled practitioners will need to perform clinical studies. As applicants stated above, skilled practitioners in the arts of drug development and medicine routinely perform such studies to

determine effective doses when bringing a new drug from the laboratory to the clinic. This is routine and reasonable experimentation. The Office has presented no evidence suggesting that a determination of effective amounts of CO, e.g., in humans, would be any less routine.

Applicants submit that a thorough examination of the specification and a rigorous application of the *Wands* factors would lead the Office to the conclusion that the present claims are in full compliance with the enablement requirement. Skilled practitioners would clearly have been able to practice the full scope of the invention recited in the claims when armed with applicants' specification and the knowledge of those of ordinary skill in the art. Accordingly, applicants request withdrawal of the rejection for lack of enablement.

Rejections Under 35 U.S.C. §102

Claims 1 to 3 and 10 to 14 were rejected as allegedly anticipated by Fujita et al., Nat. Med. 7: 598-604 (2001) (hereinafter "Fujita") or Grinstaff et al. (U.S. Patent No. 5,498,241) (hereinafter "Grinstaff"). The Office cites Bar-Or (U.S. Publication No. 2005/0215468) (hereinafter "Bar-Or") to supplement each of these rejections, apparently in an attempt to remedy the fact that neither Fujita nor Grinstaff mentions hemorrhagic shock. Applicants traverse both of these rejections for the reasons discussed below.

Fujita showed that CO improved survival of mice who had been subjected to experimentally induced lung ischemia. There is no indication in Fujita that the mice experienced hemorrhagic shock or any other type of generalized ischemia; rather, the ischemia surgically induced in them appears to have been limited to a single targeted lung (see the Methods section). The present claims are all limited to treatment of hemorrhagic shock, a condition that is not equivalent to the lung ischemia studied by Fujita.

In an attempt to establish that Fujita's disclosure anticipates the present claims, the Examiner says that Bar-Or "describes ischemia as hemorrhagic shock in a more generalized sense." Applicants understand the Examiner to be referring to Bar-Or's statement at [0004] that "[i]schemia need not be limited to one organ; it can also be more generalized (e.g., in hemorrhagic shock)." This statement in no way suggests that the word "ischemia" is understood by medical practitioners to be synonymous with "hemorrhagic shock," as the Examiner appears

to believe. In fact, such an interpretation would make no sense, since Bar-Or discusses many types of ischemia that are not "generalized" and certainly do not involve hemorrhagic shock. See, for example, Bar-Or's discussion at [0004] of "cardiovascular ischemia," "cerebral ischemia," and ischemia that occurs in individual organs such as "kidney, liver, lung, and the intestinal tract." Thus, Bar-Or cannot be taken as evidence that a reference to "ischemia" of any sort elsewhere in the art necessarily denotes hemorrhagic shock—in fact, this reference plainly indicates that organ-specific ischemia (e.g., lung ischemia) is distinct from generalized ischemia such as attributable to hemorrhagic shock. Thus, when Fujita describes treating lung ischemia experimentally induced in a mouse, one of ordinary skill would understand he is not disclosing having treated hemorrhagic shock. The rejection of the claims as anticipated by Fujita is improper and should be withdrawn.

Similarly, Grinstaff does not anticipate the presently claimed methods. Grinstaff describes compositions that are allegedly useful for *in vivo* delivery of biologics (see Grinstaff at col. 6, lines 9 to 12). The compositions include a substance (in the form of a solid, liquid or gas) in association with a polymeric shell (see Grinstaff at col. 6, lines 12 to 14). This rejection fails on several grounds, as discussed below.

First, Grinstaff does not anticipate the claims because it does not teach use of CO to treat anything. Grinstaff lists (at col. 13, line 43, through col. 14, line 26) many agents that could be included in the polymeric shells. This list mentions several gases, including CO (col. 14, lines 19-21). While this passage suggests that Grinstaff believes CO is a physiologically active substance, it does not hint at any particular use for CO. Grinstaff does not disclose any condition that might be treatable with CO, and certainly does not disclose actual use of CO.

Second, Grinstaff does not teach use of any substance, CO or otherwise, to treat hemorrhagic shock. Grinstaff does disclose use of what he refers to as "insoluble hemoglobin construct" (IHC) to treat cerebral ischemia in a rat model (see Example 28 at col. 46). Cerebral ischemia is, of course, not the same as the generalized ischemia associated with hemorrhagic shock. Nor does cerebral ischemia, a brain-specific condition, encompass hemorrhagic shock.

Thus, even if Example 28 taught use of CO instead of IHC, it would not anticipate the present claims.

Third, the disclosure in Example 28 that an oxygen-bearing substance such as IHC can be useful for delivering oxygen to an oxygen-starved (i.e, ischemic) brain is certainly not a disclosure that ischemia can also be treated with CO. CO's toxicity is, of course, attributable to its inactivation of hemoglobin. One of ordinary skill, aware of CO's effects on hemoglobin, would assume that CO would only make ischemia worse by inactivating hemoglobin in the patient's blood. It would certainly not be expected to improve oxygenation. Accordingly, it would make no sense to combine the mention of CO at col.14, line 20, with the teaching of a use for IHC to treat cerebral ischemia at col. 46.

Thus, for numerous reasons, Grinstaff does not anticipate the claims.

Claims 1 to 3 and 10 to 14 were rejected as allegedly anticipated by Pinsky et al. (US Publication No. 2005/0048133). According to the Office action, "Pinsky treats tissues damaged...by ischemic disorders...with carbon monoxide inhalation." Applicants traverse this rejection.

Pinsky recites at [0059] that:

> "[I]schemic disorder" encompasses and is not limited to a peripheral vascular disorder, a venous thrombosis, a pulmonary embolus, a myocardial infarction, a transient ischemic attack, lung ischemia, unstable angina, a reversible ischemic neurological deficit, adjunct thromolytic activity, excessive clotting conditions, sickle cell anemia or a stroke disorder.

Each of the conditions listed in the quoted text involves ischemia at a discrete site. Pinsky fails to teach treating hemorrhagic shock – a condition brought on by a loss of circulating blood volume and/or oxygen carrying capacity and resulting in global insult to all organ systems. Nowhere does Pinsky even mention the term "hemorrhagic shock" or anything equivalent thereto, much less teach, or even suggest, that CO could be used to treat this disorder. Because Pinsky fails to teach or suggest all elements of applicants' methods, it does not anticipate the pending claims.

Applicants therefore request that the rejections of the claims for anticipation by Fujita, Grinstaff, and Pinsky be reconsidered and withdrawn.

CONCLUSION

Applicants submit that all pending claims are in condition for allowance, which action is requested.

Also enclosed is a Petition for Three Month Extension of Time. Please apply the charge of $1020 for the required fee to Deposit Account No. 06-1050. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 14022-011001.

Respectfully submitted,

Date: July 11, 2007

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